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Redefining Unexplained Anemia in Elderly

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Some information, however, can be gleaned from the results reported in our study. First, the median (interquartile range [IQR]) serum testosterone level in our treated cohort during follow-up was 318 (237-435) ng/dL compared with the untreated population with a median (IQR) 212 (160-253) ng/dL; testosterone replacement therapy resulted in a significant increase in serum levels with over half of the patients normalizing their serum testosterone levels. Second, although we did not generate a Framingham Risk Score for the patients in our study,¹ we did conduct a stratified analysis restricted to men with baseline cardiovascular risk factors and the results from this stratified analysis were consistent with our overall study findings. Third, we have seen the beneficial effects of treating hypertension or hyperlipidemia in our population in recent years,³ suggesting that this could affect our results. Thus, we included calendar year in our adjusted models and found a lower risk of cardiovascular outcomes over time potentially related to changing treatment patterns and/or length of follow-up.

We believe the questions posed by Stavropoulos and colleagues probe important nuances about the potential relationship between testosterone replacement therapy and cardiovascular disease outcomes. Undoubtedly, further focused studies based in other cohorts of men, from different settings, could provide important new insights.

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Conflict of Interest Disclosures: None reported.

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Redefining Unexplained Anemia in Elderly

To the Editor The Original Investigation by Roy et al¹ recently published in *JAMA Internal Medicine* showed in a well-executed double-blind placebo-controlled trial the efficacy of testosterone supplementation in correcting anemia among older men with low testosterone concentrations. The authors concluded that testosterone supplementation is a feasible approach to increase hemoglobin levels of both unexplained anemia as well as anemia from known causes. The authors first defined known causes of anemia by choosing specific cut-off values and subsequently categorized the remaining group of

patients as having an unexplained anemia. However, regarding 2 known causes of anemia, we question whether the authors did not underestimate its prevalence.

First, to define iron deficiency, Roy et al¹ used a serum ferritin level of lower than 40 ng/mL. However, it has been established² that iron deficient erythropoiesis occurs in elderly patients with a serum ferritin level of up to 75 ng/mL, which is nearly the double of the currently chosen cut-off value. Therefore, a portion of the patients currently labeled as having an unexplained anemia can still be classified as being iron deficient.

Second, to define vitamin B₁₂ deficiency Roy et al¹ selected all patients with a vitamin B₁₂ level of lower than 200 pg/mL. Yet, it should be realized that serum levels of vitamin B₁₂ are maintained for a long time at the expense of vitamin B₁₂ stores. As a result, diagnosis of vitamin B₁₂ deficiency is often delayed and underestimated. Hence, the important Framingham study³ used a cut-off value of 350 pg/mL to define vitamin B₁₂ deficiency in elderly patients which is more realistic to fully capture vitamin B₁₂ deficiency.

Subanalyses in which these cut-off values for iron deficiency and vitamin B₁₂ deficiency, both highly prevalent in elderly populations, are taken into account could potentially further strengthen the reported results by Roy et al.¹ Finally, we would like to mention that the beneficial effect of correcting unexplained anemia through testosterone supplementation might be attributable to down-regulation of serum hepcidin, the master regulator of iron homeostasis. Previous studies have revealed that elderly with an unexplained anemia have elevated levels of serum hepcidin.⁴ Because testosterone is known to be a prominent suppressor of serum hepcidin,⁵ it is likely that serum hepcidin will decrease, and subsequently, iron availability will improve and lead to a more effective erythropoiesis. Future studies evaluating the effect of testosterone supplementation on hemoglobin levels might want to consider measuring serum hepcidin as putative mechanism.

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Conflict of Interest Disclosures: None reported.

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In Reply We appreciate the comments of Eisenga et al regarding our classification of the anemias in our Original Investigation.¹ They question our choices of the levels of ferritin and B₁₂ used to classify patients as iron-deficient or Vitamin B₁₂-deficient, respectively. Their questions raise the more general issue that there is no universally accepted cut-off level by which either anemia can be diagnosed using a single test. We concede that we might have misclassified a few participants in either direction for each type of anemia.

With respect to iron deficiency, others have suggested that ferritin values in the general range we selected (<40 ng/mL) are reasonable for a presumptive diagnosis of iron deficiency anemia.² Indeed in the study cited by Eisenga et al,³ ferritin levels 45 to 75 ng/mL were suspected to be related to iron deficiency only on the basis of blood film evaluation, not the demonstration of absent iron stores, as was the case for those with levels less than 45 ng/mL. Even some patients whose levels were less than 45 ng/mL had iron stores present. Thus misclassification may occur in either direction. Similarly, B₁₂ levels have limited sensitivity and specificity, and while a value of less than 200 ng/L more likely indicates true deficiency than higher levels, some individuals whose values are greater than 200 ng/L could have relative B₁₂ deficiency.^{4,5} Whether this mild deficiency would be sufficient to cause anemia is uncertain.

Nevertheless, while some degree of misclassification may have occurred, because testosterone treatment corrected anemias of “known” cause as well as unexplained anemia, our conclusion that testosterone improves both types of anemia in older men who have low testosterone appears solid. We emphasize that this conclusion applies only to older men with low testosterone and not to men who are anemic but have normal testosterone.

With respect to the suggestion by Eisenga et al regarding the mechanism by which testosterone increased hemoglobin, we agree that testosterone may have acted by suppressing hepcidin.⁶

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Conflict of Interest Disclosures: None reported.

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Intensive Blood Pressure Control on Gait Speed and Mobility Limitation for Older Adults

To the Editor In the SPRINT (Systolic Blood Pressure Intervention Trial) randomized clinical trial published in a recent issue of *JAMA Internal Medicine*, Odden and colleagues¹ conclude that intensive blood pressure lowering was not associated with changes in gait speed or transitions in mobility status among adults 75 years or older. SPRINT¹ is an important randomized clinical trial that should have a substantial influence on future clinical practice. However, it was not well designed to test the effect of intensive blood pressure control on gait speed and mobility limitation in older adults.

First, according to the registration (NCT02106234), the main outcomes (gait speed and mobility limitation) of this article were not prespecified, because none of them were submitted in the registration. This limitation can lead to a selective outcome of the authors' intervention.

Second, the sample of older people in SPRINT¹ may not be representative of the general older population. Odden et al acknowledged that SPRINT excluded individuals with a history of diabetes or stroke, symptomatic heart failure, dementia, or an indication for specific antihypertensives. But these comorbidities have a population prevalence in elderly patients, with rates that continue to increase.^{2,3} Additionally, the only ambulatory, community-based persons were recruited into the study.¹ Therefore, the results do not generalize to many older people with multiple coexisting conditions, frailty, and disabilities.

Third, it is also important to note that no information was provided about functional limitations, cognitive impairment, hearing or visual problems, and balance or postural disorders between the groups. These are generalizable to the older population, but may render the gait speed test more time-consuming than expected, representing a possible bias.⁴

Fourth, the authors did not report adverse events in older patients between the intervention and control groups. In the original SPRINT,⁵ serious adverse drug events occurred more frequently in the aggressively treated group, with an increase from 2.5% to 4.7% (hazard ratio, 1.88; *P* < .001).

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